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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,192	COOPER ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-123* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19, 26, 28, 30-31, 34-42, 51-82, 103-104, 106-109, 114-117, and 122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8 Sept 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8 Sept 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 20-25,27,29,32,33,43-50,83-102,105,110-113,118-121 and 123.

DETAILED ACTION

Election/Restrictions

Examiner acknowledges the election of species of nucleic acid complexes directed to having components including cDNA, CK15-60P10, and acetate, in the reply filed on 23 June 2006.

Claim Status

Claims 1-123 are pending. Claims 20-25, 27, 29, 32-33, 43-50, 83-102, 105, 110-113, 118-121, and 123 are withdrawn because they are drawn to non-elected species. Claims 1-19, 26, 28, 30-31, 34-42, 51-82, 103-104, 106-109, 114-117, and 122 are under current examination.

Oath/Declaration

The oath has been reviewed by the examiner. The petition requesting removal of an inventor has been forwarded to the Petition Branch for review.

Specification

The use of the trademark PLAS*min*™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 11 May 2006 consisting of 3 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit from U.S. Application No. 2002/0042388 (abandoned), filed 31 May 2001, provisional U.S. provisional Application No. 60/287,419, filed 31 May 2001, and U.S. provisional Application No. 60/207,949, filed 31 May 2000. The instant application has been granted the benefit date, 31 May 2000, from the application 60/207,949. However, it must be noted that the provisional application makes no mention of lyophilization or disaccharides.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 26, 28, 30-31, 34-42, 51-82, 103-104, 106-109, 114-117, and 122 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some 'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

In the instant case, claims 1-19, 26, 28, 30-31, 34-42, 51-82, 103-104, 106-109, 114-117, and 122 provide for no other shape except rod-shaped complexes. However, the instant application is not enabled for a composition wherein said complexes are all rod-shaped particles nor is the application enabled for a method of separating rod-shaped from all other shaped particles. There is insufficient support in the specification for this limitation.

Most of the specification is drawn to compositions wherein said complexes are in the shape of a condensed sphere. Additionally, there is some support in the specification for compositions wherein the shapes of the complexes are a mixture of shapes, including spheres, toroids, relaxed toroids, toroids with tails, Y-shaped rods, small and large rods. Therefore, the nature of the invention seems to be for compositions that are more than merely rod-shaped complexes. In fact, the electron micrographs provided in the drawings of the instant application show mixtures of shapes (see Figure 10, Acetate panel and Figure 13 and Figure 17). Furthermore, Kwoh et al. teach "PLLs of all sizes condensed plasmid DNA into toroidal and rod-shaped structures" (page 179, section 3.4), indicating that the state of the art teaches a mixture of shapes is usual outcome of condensation methods that use PLL. Nowhere, in the working examples, of the instant application is there support for or instructions detailing how to make a composition of complexes that are only rod-shaped nor is a method of separating rod-shaped from other shaped particles described in the specification.

The examiner cannot understand from the specification why the invention is directed to only rod-shaped complexes. Furthermore, the specification does not teach why the particular sizes and shapes are important to the invention.

Therefore, the quantity of experimentation required to make and use the invention, as claimed, is insufficient to enable the invention.

In the instant case, claims 1-19, 26, 28, 30-31, 34-42, 51-82, 103-104, 106-109, 114-117, and 122 are directed to nucleic acid-polymer particles and methods of gene delivery to cells. The specification states, "the present invention provides a method of preventing or treating a disease or other clinical condition in a subject." (page 4,line 28-29). Implicitly, the intended use of these products and methods are for gene therapy. In particular, the specification teaches in Example 2, "therapies for pulmonary diseases, such as cystic fibrosis" (page 9, line 21-22). However, there is insufficient support in the specification for gene therapy applications.

In view of the state of the art and the level of the skilled in gene therapy art, it is still under development and highly unpredictable. *Orkin et al.* (NIH Report, 1995 Dec) reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) one cannot predictably extrapolate the result

of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; and 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints (pages 1-2). Although the reference is from a few years before the provisional application (60/207,949), the general status of gene therapy art has not significantly changed. *Patterson* (STATEMENT OF AMY PATTERSON M.D., February 2000) reviews "THE SUCCESS OF THIS TECHNOLOGY [GENE THERAPY] IS DEPENDENT UPON NOT ONLY THE DELIVERY OF GENETIC MATERIAL INTO THE TARGET CELLS, BUT ALSO THE EXPRESSION OF THE GENE ONCE IT REACHES ITS TARGET SITE. BOTH OF THESE REQUIREMENTS POSE CONSIDERABLE TECHNICAL CHALLENGES". *Patterson* further teaches that out of 372 clinical trials registered with the NIH, only one percent of the trials (3) have progressed to Phase III efficacy studies. "FOR THIS REASON, IT IS PERHAPS MORE ACCURATE TO REFER TO THIS TECHNOLOGY AS 'GENE TRANSFER', RATHER THAN 'GENE THERAPY', UNTIL THERE IS MORE EVIDENCE FOR THE THERAPEUTIC BENEFIT OF THIS TECHNOLOGY".

In particular to the disease referenced in the instant application, Ferrari et al. (Advanced Drug Delivery Reviews 54 (2002) 1373–1393) state, "Clinical trials of gene therapy for cystic fibrosis suggest that current levels of gene transfer efficiency are probably too low to result in clinical benefit, largely as a result of the barriers faced by gene transfer vectors within the airways" (Abstract). Furthermore, "respiratory epithelium has evolved a complex series of extracellular barriers (mucus, lack of receptors, immune surveillance, etc.) aimed at preventing penetration of lumenally

delivered materials, including gene therapy vectors" (Ferrari et al, Abstract). Essentially, the art teaches that the targeting of therapeutic genes to desired tissue or cells and transfection efficiency are major obstacles. Ferrari et al. indicate that "well differentiated, non-dividing airway epithelial cells show very low transfection efficiency" (page 1380, section 4.3). Another difficulty common to gene therapies of Cystic Fibrosis involves generating prolonged expression, "One of the main obstacles to the development of gene therapy for the airways is the inability of current viral and nonviral gene transfer vectors to direct sustained expression of a therapeutic transgene" (Ferrari et al., page 1384, section 6). The lack of prolonged expression can be due to loss of vector, transcriptional silencing, and generation of an immune response. Therefore, the high level of unpredictability involving non-viral gene therapy approaches for Cystic Fibrosis makes any therapeutic approach for this disease uncertain.

The instant application does not overcome the difficulties intrinsic to gene therapy treatments of Cystic Fibrosis. While the specification teaches the concept of overcoming the targeting difficulties discussed in the art above, by using targeting ligands to enhance nuclear or receptor targeting, the instant application does not identify particular targeting moieties that would be useful for treating Cystic Fibrosis. Additionally, a therapeutic gene specific for Cystic Fibrosis has not been identified in the instant application. Furthermore, there is no mention in the specification of how the instant invention addresses the need for prolonged gene expression in a successful non-viral gene therapy. Nor does the specification address the common problem of loss of the vector. Although the instant specification does teach particles and methods for

enhancing gene delivery, it has not overcome some of the basic obstacles that are common to gene therapy for Cystic Fibrosis.

Therefore, the quantity of experimentation required to make and use the invention, as claimed, is insufficient to enable the invention for gene therapy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The invention as claimed is directed to a product-by-process. The implication of this is that the product is the subject of examination, without regard to the process of producing it. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) MPEP 2113.

Claims 1-2, 8-9, 11-12, 17, 20, 26, 28, 38 and 102-104, are rejected under 35 U.S.C. 102(b) as being anticipated by Wolff et al (US-6,126,964).

Claim 1 is directed to a "composition comprising unaggregated nucleic acid complexes...consisting essentially of...nucleic acid molecule and...polycation...counterion...of acetate...are rod-shaped when visualized by transmission electron microscopy." Broadly read, claim 1 is being interpreted to mean any rod shaped composition comprising the elements recited. Wolff et al. teach "DNA-polycations complexes" (column 1, line 18), "counterion" (column 2, line 67), "acetate" (column 22, line 22) which are "rods" (column 2, line 47) and have a distinct structure from the "large aggregates" (column 2, line 49). Furthermore, Wolff et al teach "transmission electron microscopy of the formed complexes" (column 13, line 49).

Claims 2, 9, 30, 34, 36, are directed to "polycation molecules are polylysine." Wolff et al teach "cationic proteins could be...polylysine" (column 10, lines 43-44).

Claim 8 adds the further limitation not included in claim 1 that the "nucleic acid encodes at least one functional protein." Wolff et al teach "DNA can produce...a therapeutic protein" (column 9, lines 56-57).

Claim 11 is directed to "promoter which controls transcription of an RNA molecule encoding...functional protein." Wolff et al teach "plasmid expresses...luciferase from the...promoter" (column 13, lines 17-19). The art understands that transcription of RNA must occur for a protein to be expressed from a plasmid.

The limitation of claim 12, "protein is therapeutic" is also met by Wolf et al. "DNA can produce...a therapeutic protein" (column 9, lines 56-57).

Claim 17 adds the further limitation to claim 1 of "cDNA." Wolff et al teach "cDNA" (column 13, line 20).

Claim 20 adds the further limitation to claim 1 of "antisense." Wolff et al teach "DNA can produce...anti-sense RNA" (column 9, line 56-57).

Claim 23 adds the further limitation to claim 1 of "nucleic acid molecule is an RNA molecule." Wolff et al teach "nucleic acid including...RNA" (column 9, line 55).

Claim 26 adds the further limitation to claim 1 of "soluble...complexes" and "salt concentration." Wolff et al teach a "truly soluble complex" (column 16, line 2) and "salt and ionicity conditions" (column 4, line 31).

Claim 28 adds the further limitation to claim 1 of "absence of added salt." Wolff et al teach that "this solution can be water" (column 10, line 2).

Claim 38 is directed to "complexes...associated with a lipid." Wolff et al. teach "DNA (that was within polymer particles) was transfected...with a cationic lipid" (column 12, lines 44-46).

Claims 102-104 are directed to complexes "associated with a lipid." Wolff et al. teach complexes can contain other compounds in addition to DNA and polymer, including "lipids" (column 10, line 52).

Accordingly, Wolff et al. anticipated the instant claims.

Claims 1-2, 8-9, 11-12, 17-18, 26, 28, 30, 34, 36, 38, 53, 65, 78, 85, 92 and 102-103 are rejected under 35 U.S.C. 102(b) as being anticipated by Hanson et al. (US Patent 5,844,107).

Claims 1-2 are directed to a rod-shaped condensed polylysine/nucleic acid complex, comprising an ion of acetate, as measured by transmission electron microscopy.

Hanson et al teach a rod-like (column 62, line 53) condensed polylysine/DNA complex (column 52, line 1-2) without aggregation (column 64, line 60) comprising a single nucleic acid (column 65, line 3) further comprising an ion of acetate (column 22, line 4), as measured by electron microscopy (column 65, line 23). Table 104 in Hanson teaches polylysine/DNA complexes having 10-56 lysine residues (column 59, lines 25-50).

Hanson et al. teach the further limitation of claim 8-9, 11-12, 53, 65, 78, 85, 92 "a targeting moiety" in their Abstract, "targeting may be enhanced by means of a target cell-binding moiety." The further limitations of claims 8-9 and 11, "nucleic acid...encodes... functional protein" are taught by Hanson et al. "protein product" (page 17, column 46). The limitations of claim 12 that the protein product is "therapeutic" are taught by Hanson et al. "therapeutic effect" (column 4, line 62), more explicitly listing therapeutic genes, "coagulation factors...enzymes...receptors" (column 16, lines 40-48). Hanson et al. teach the limitation of claim 11, "promoter" (17 column, line 41).

Hanson et al. teach the limitation of claims 17-18, "cDNA" (16 column, line 49).

Claims 26, 30, and 36 are directed to "a salt concentration sufficient for compaction of the complexes." Hanson et al. teach "critical salt concentration" (column 5, line 7). The further limitation of claims 26, 30, and 36, "soluble compacted complexes" is also taught by Hanson et al, "non-naturally occurring soluble compacted complexes of a nucleic acid and a carrier molecule" (column 66, lines 36-37).

Claim 28 and 34 are directed to "absence of salt". Hanson et al. teach, "initial salt concentration could be as low as zero" (column 23, line 27).

Claim 38 and 102-103 is directed to "associated with a lipid." ". Hanson et al. teach "complexes with lipids" (column 66, line 12).

Accordingly, Hanson et al. anticipated the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3, 10, 19, 31, 35, 37, 51-53, 63-65, 67-68, 76-78 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanson et al. (US Patent 5,844,107) in view of Park et al. (US Patent 6,177,274) and Schacht et al. (WO/1998/19710).

Claims 3, 10, 19, 31, 35, 37, 51-53, 63-65, 67-68, 76-78 and 104 are directed to complexes having polylysine of 15-60 residues conjugated to PEG through a cysteine residue.

The teachings of Hanson et al. are described above in the 35 USC 102(b) section. In addition, Hanson et al. teach the limitation of claim 53, 65, 78, "a targeting moiety" in their Abstract, "targeting may be enhanced by means of a target cell-binding moiety." Also, Hanson et al. teach the further limitations of claim 67 "nucleic acid...encodes...functional protein" are taught by Hanson et al. "protein product" (page 17, column 46). The limitation of claim 68 that the protein product is "therapeutic" are taught by Hanson et al. "therapeutic effect (column 4, line 62), more explicitly listing therapeutic genes, "coagulation factors...enzymes...receptors" (column16, lines 40-48.

Hanson et al. does not teach Polyethylene Glycol (PEG) joined to 15-60 lysine residues through an N-terminal cysteine linkage where the PEG has an average molecular weight of 10kD.

Park et al teach incorporation of a PEG of molecular weight 0.5 to 20 kD (column 5, line 29) to the polylysine with the length of 10-250 lysine residues (column 6, line 2-3) through an amino terminal linkage (column 5, line 28).

However, Park et al. do not teach a cysteine moiety that has been incorporated to the N-terminus of the polylysine so as to provide a bridge for attachment to the PEG.

Schacht et al. teach incorporation of a PEG of molecular weights 2kD (page 38, line 19) and 5 kD (page 46, line 14) and 16kD (Figure 4) to the polylysine of molecular mass 4 to 20 kD (intrinsic length of 27 to 137 lysine residues (page 10, line 12) through an amino terminal linkage using a disulfide bond (page 25, lines 22-35).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Hanson et al. with Park et al. further in view of Schacht et al. to link any PEG with MW of 10kD to one or more polycationic agent such as polylysine, having more than at least 15 to 60 residues with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to incorporated any known PEG species to a polycationic moiety contained in the DNA complex of Hanson et al because the concept of utilizing a polycationic polylysine (PLL) linked to PEG whereby PEG-PLL functions as an enhanced linker so as to link the backbone of the PLL to a bioactive molecule or the ligand to a cell of interest (targeting moiety) is well

taught by Park, and because Park teaches that PEG linked to PLL even further enhances the delivery of a charged therapeutic agent across the bilayer membrane of a target cell. Furthermore, the person of ordinary skill in the art would have been motivated to make those modifications because both Park and Schacht teach that PEG linked to PLL enhance the delivery of a charged therapeutic agent across the bilayer membrane of a target cell. (Park, column 11, line 46-52 and Schacht, page 2, line 7).

Insofar as the limitation of an incorporation of a reactive group such as a cysteine residue at the N-terminal of a polylysine, which terminal is further linked to a protective hydrophilic polymer such as PEG, the use of any reactive group including the use of a disulfide bond from any well-known source, e.g., cysteine, is also taught in the Schacht reference (page 25, line 22).

It would have been obvious for one of ordinary skill in the art to have further modified the N-terminal of the polylysine by providing a disulfide bridge so as to act as a bridge for PEG's linkage. One of ordinary skill in the art would have been motivated to employ a cysteine, which is well known in the art as a source of disulfide bond used as an attachment point for a reactive group because such use of any reactive group including the use of a disulfide bond from any source is also taught by the Schacht reference.

Claims 58-62, 66, 73-75, 79-82, 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanson et al. (US Patent 5,844,107) in view of Park et al. (US

Patent 6,177,274) and further in view of Schacht et al. (WO/1998/19710) as applied to claims 3, 10, 19, 31, 35, 37, 51-53, 63-65, 67-68, 76-78 and 104 above, and further in view of Mao et al. (Journal of Controlled Release 70 (2001) 399–421).

Claims 58-62, 66, 73-75, 79-82, 122 are directed to lyophilization and resuspension of complexes prior to treatment of cells.

Hanson et al. teach the further limitation of claim 61, 75, 82 that "nucleic acid is delivered to and taken up by cells." Hanson et al teach "DNA molecules taken up by each cell." (column 13, lines 21). Park et al further teaches the limitation of claim 61, 75, 82 that "nucleic acid is delivered to and taken up by cells." Park et al teach "composition enters said cells, and the nucleic acid of said composition is released." (column 16, lines 1-4). Also, Hanson et al. teach the further limitations of claims 67, 75, 82, "nucleic acid...encodes...functional protein" are taught by Hanson et al. "protein product" (page 17, column 46). The limitation of claim 68 that the protein product is "therapeutic" are taught by Hanson et al. "therapeutic effect (column 4, line 62), more explicitly listing therapeutic genes, "coagulation factors...enzymes...receptors" (column16, lines 40-48.

Furthermore, Hanson et al teach the limitation of claims 62, 74, 81, 122 that the delivery method does not use a disaccharide, writing, "one class of ligands...are carbohydrates, especially...oligosaccharides...another class of ligands...are peptides" (column 14, line 26-31).

The Hanson, Park, and Schacht references do not teach lyophilization of the complex. Park et al. also does not teach the methods of delivery where the composition does not contain a disaccharide (claims 62, 74, 81, 122).

Mao et al. teach lyophilization of the complex and administration of the complex to cells (page 419). It is clear from the art and context of the reference that the complex is resuspended prior to administration.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to lyophilize the DNA-PEG-polylysine complex and to later resuspend it in order to administer it to cells.

The person of ordinary skill in the art would have been motivated to make that modification to lyophilize and resuspend the instant invention because it is an art established method of preserving non-viral gene therapy products prior to clinical use. An artisan would have expected success, because the art was aware of these techniques and was using them by the time of the instant application.

Therefore the method as taught by Hanson et al. with Park et al. and Schacht et al. and in further view of Mao would have been *prima facie* obvious over the method of the instant claims.

Claims 4-7, 13-16, 39-42, 54-57, 69-72, 106-109, and 114-117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanson et al. (US Patent 5,844,107) in view of Park et al. (US Patent 6,177,274) and further in view of Schacht et

al. (WO/1998/19710) as applied to claims 3, 10, 19, 31, 35, 37, 51-53, 63-65, 67-68, 76-78 and 104 above, and further in view Kwoh et al. (Biochimica et Biophysica Acta 1444 (1999) 171-190).

Claims 4-7, 13-16, 39-42, 54-57, 69-72, 106-109, and 114-117 are directed to transmission electron microscopic characterization of the rod-shaped complexes. In particular, the instant claims are directed to the limitation that the condensed particles have a rod-shape when viewed by electron microscopy and that the rods have a length of 100-300 nm and a diameter of 10-20 nm, Kwoh et al. teach these limitations.

Kwoh et al. teach "PLLs of all sizes condensed plasmid DNA into toroids and rod-shaped structures...as shown by electron microscopy...ranging in size...from 40 to 80 nm for rods" (page 179, section 3.4). Furthermore, Kwoh et al teach that with conjugation of PEG to the PLL-DNA complexes, the sizes of the rods are larger; "rod structures observed in electron micrographs of PLL10K-PEG5K polyplexes were longer and more abundant than rods observed with PLL polyplexes" (page 183). Figure 8B (page 184) show rod-like PLL-PEG-DNA structures in the electron micrographs that are about 200nm in length. Furthermore, in regard to the limitation of the instant claims that the diameter of the rod-shaped complexes is 10-20 nm, Figure 8D (page 184, center panels) shows a comparison of a PLL-PEG/DNA rod-shaped complex and a small spherical particle 25 nm in diameter (indicated with closed arrowhead)" (page 184). It is clear that the diameter (width) of the rod is slightly smaller than the diameter of the small spherical particle. Although an exact measurement of the diameter (width) of the rod-shaped complexes in the Kwoh et al article are not explicitly described, the sizes

are of the rod-shaped complexes shown in electron micrographs fit within the approximate sizes of the instant claims, 4-7, 13-16, 39-42, 54-57, 69-72, 106-109, and 114-117.

It would have been obvious for one of ordinary skill in the art to combine the inventions of Hanson et al. and Park et al. and Schacht et al. with the invention of Kwoh et al. in order to characterize the size and shape of the PLL-PEG-DNA complexes using transmission electron microscopy as in Kwoh et al. because it is a standard method employed by those companies and laboratories studying new methods of formulating DNA for non-viral gene therapy. One of ordinary skill in the art would have been motivated to employ electron microscopy to characterize the complexes, because it is well known in the art as method of establishing the size and conformation of the particles.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Hanson et al. and Park et al. and Schacht et al. and Kwoh et al. because the art teaches disulfide linkages were successfully performed between PEG and PLL and characterizing the complexes by electron microscopy has been performed for this purpose many times by many different inventors and researchers.

Therefore the techniques as taught by Hanson et al. in view of Park et al. and Schacht et al. and further in view of Kwoh et al. would have been *prima facie* obvious over the compositions and methods of the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19, 26, 28, 30-31, 34-42, 51-82, 103-104, 106-109, 114-117, and 122 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 41-43, 93-94, 96-97, 155-159, 182 of U.S. Patent Application No. 20030134818. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 41-43, 93-94, 96-97, 155-159, 182 of the cited application are directed to methods of preparing a composition of nucleic acid-PEG-PLL complexes, having counterion of acetate, and characterized by electron microscopy. Claims 1-19, 26, 28, 30-31, 34-42, 51-82, 103-104, 106-109, 114-117, and 122 of the instant application are

directed to the product created by the process of the cited application. Furthermore, the specifications for the two applications appear to be identical.

Accordingly, instant claims and the claims of the cited application are obvious variants. Therefore, the inventions as claimed are co-extensive.

Claims 1-19, 26, 28, 30-31, 34-42, 51-82, 103-104, 106-109, 114-117, and 122 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-14, 16-19, 184, 199-200 of U.S. Patent Application No. 20030171322. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 10-14, 16-19, 184, 199-200 of the cited application are directed to methods of preparing a composition of nucleic acid-PEG-PLL complexes, having counterion of acetate, and characterized by electron microscopy. Claims 1-19, 26, 28, 30-31, 34-42, 51-82, 103-104, 106-109, 114-117, and 122 of the instant application are directed to the product created by the process of the cited application. Furthermore, the specifications for the two applications appear to be identical.

Accordingly, instant claims and the claims of the cited application are obvious variants. Therefore, the inventions as claimed are co-extensive.

Conclusion

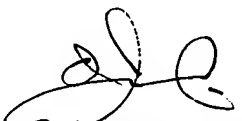
No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave Nguyen** can be reached on **571-272-0731**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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